DEVELOPMENT OF HEALTH CRITERIA FOR SCHOOL SITE RISK ASSESSMENT PURSUANT TO HEALTH AND SAFETY CODE SECTION 901(g):

PROPOSED CHILD-SPECIFIC BENCHMARK BLOOD LEAD CONCENTRATION FOR SCHOOL SITE RISK ASSESSMENT

Public Review Draft Report
March 2006

Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Executive Summary

This document proposes a new child-specific health guidance value (HGV) for lead of an increase of 1 microgram lead per deciliter of blood (µg/dl). The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop child-specific HGVs for use in health risk assessment at school sites pursuant to Health and Safety Code Section 901(g). In the case of lead, the HGV is termed a child-specific benchmark blood lead concentration (BC_B). The BC_B for lead is not an absolutely safe exposure level, since no safe level has been definitively established. One µg/dl is a lower-bound estimate of an incremental increase in children's lead blood level (Pb_B) that is estimated to decrease Intelligence Quotient (IQ) by 1 point. It is based on an analysis of recent reports relating neurobehavioral deficits to Pb_B at concentrations lower than in previous reports. In developing the BC_B, OEHHA recognized that the ideal would be no additional exposure to environmental lead since many children today have lead blood levels above the level where deficits in IQ can be measured. However, from a practical standpoint, a BC_B of zero would not be useful. Changes in blood lead levels below the adopted BC_B are expected to cause no measurable adverse effect, although a very small adverse effect theoretically does occur at the BC_B. A 1-µg/dl increase in Pb_B corresponds to an increased daily intake of 6 µg of ingested soluble lead, or 5 µg of inhaled lead. OEHHA suggests that the Department of Toxic Substances Control's Leadspread model be used to estimate acceptable lead levels in soil and other media.

Introduction: Mandate and Methodology

Health and Safety Code (HSC) Section 901(g), requires the Office of Environmental Health Hazard Assessment (OEHHA), in consultation with the appropriate entities within the California Environmental Protection Agency, to (1) identify chemical contaminants that are commonly found at school sites and determined by OEHHA to be of greatest concern based on criteria that identify child-specific exposure and child-specific physiological sensitivities, and (2) publish and make available to the public and other state and local environmental and public health agencies and school districts, child-specific numerical health guidance values (HGVs) for those chemical contaminants. HGVs established by this process are intended for use in assessing risk at proposed or existing California school sites, which may include pre-school and day-care children. They are not intended for use in clinical settings, or for population screening. HGVs are subject to review and refinement as the state of the science progresses.

Pursuant to HSC §901(g), in June 2002, OEHHA issued a report, "Development of Health Criteria for School Site Risk Assessment Pursuant to HSC Section 901(g): Identification of Potential Chemical Contaminants of Concern at California School Sites," documenting the process by which OEHHA would identify chemicals meeting those two criteria and compiling a list of 78 chemicals that meet the two criteria. The report is available at http://www.oehha.ca.gov/public_info/public/kids /schoolsrisk.html. OEHHA has issued reports on HGVs for nickel, cadmium, chlordane, heptachlor, heptachlor epoxide, and methoxychlor, and has issued draft reports on manganese, atrazine, deltamethrin, pentachlorophenol, and endosulfan, which are all available at: http://www.oehha.ca.gov/public_info/public/kids/index.html.

Development of a HGV begins with the selection of high-priority chemicals from the compilations generated in Phase I, as described in the June 2002 report. Chemicals are high-priority if 1) they have been found at school sites in California, 2) they have possible adverse effects in organ systems that are still developing during childhood, and, 3) they have been identified as a concern by other OEHHA programs, 4) they are carcinogens and their existing RfD approximates the dose associated with a 10^{-4} lifetime cancer risk, and 5) appropriate quantitative health effects data are available. For the selected chemicals, OEHHA evaluates published studies to define a dose/response relationship for the kinds of effects to which children may be more sensitive, using these data to develop a HGV. HGVs are termed children's reference doses (chRD) if they are expressed as a dosage and children's reference concentrations (chRC) if they are expressed as a concentration in air. Since this is neither, we are proposing the term children's benchmark concentration in blood (BC_B).

Basis for Selection of Lead

Lead (Pb) meets both of the criteria for selection in HSC §901(g): it is commonly found at school sites and it is of concern based on criteria that identify child-specific exposure and child-specific physiological sensitivities. Lead is the third most frequently detected chemical at school sites having Preliminary Endangerment Assessments reviewed by the Department of Toxic Substances Control. The California Department of Health Services and the California Air Resources Board studied lead contamination at schools. Their report is available at: http://www.dhs.ca.gov/ps/deodc/childlead/schools/sitemap.htm. Young children are more sensitive to the effects of environmental lead than adults because they receive higher exposures in proportion to their smaller body size, and they absorb a higher percentage of the lead they ingest (Rabinowitz et al., 1974, Ziegler et al., 1978). Fetuses, neonates, and children are also more sensitive to the effects of Pb than adults because Pb affects the developing nervous system at levels that apparently do not affect the mature nervous system (Needleman, 1982). Koller (2004) concluded that there is no margin of safety at existing exposures.

OEHHA reviewed the toxicology of lead during the review of lead as a Toxic Air Contaminant, and during the development of the Public Heath Goal for drinking water (OEHHA, 1997a, 1997b). This document is not intended to be a complete review of the abundant relevant literature on the toxicology of lead; rather, it emphasizes selected articles appearing since those reviews.

Occurrence, Use, Chemistry, and Environmental Fate

Lead, with an atomic number of 82, occurs in four stable isotopes: 204, 206, 207, and 208. Ratios of these isotopes have been used as "fingerprints" to help identify sources of environmental lead. Lead's density, malleability, ductility, resistance to corrosion, and poor electrical conductivity, make it useful in several industries (CARB, 1997). Its concentration in California soils analyzed by Bradford et al. (1996) ranges from 12 to 97 mg/kg. Environmental contamination with lead is most often the result of its use in paints, gasoline, ceramics, plumbing products, solder, storage batteries, ammunition, and herbicides.

Toxicology

Existing Health Criteria

The Centers for Disease Control (CDC)(1991) determined that primary prevention activities in children should begin at 10 µg/dl, based on the body of evidence available at that time.

The Food and Drug Administration's (FDA) tolerable daily dietary lead intake for children under age 6 is 6 µg (http://www.cfsan.fda.gov/~dms/fdalead.html).

The Agency for Toxic Substances and Disease Registry (ATSDR) has not developed a Minimal Risk Level (MRL) for lead. The lowest effect levels reported by ATSDR (1997) are 6.5 µg/dl, based on lower scores on tests of cognitive function, 3 to 56 µg/dl, based on decreased aminolevulinic acid dehydratase, and 7.7 µg/dl, based on reduced growth.

The California Air Resources Board (CARB), (1997) identified lead as a toxic air contaminant based on its neurobehavioral effects in children and neonates, blood pressure effects in adults, and possible carcinogenicity. OEHHA, (1997b) estimated that each 1 µg/dl increase in Pb_B in children over 5 years of age would result in an average decline of 0.33 points of full-scale IQ

OEHHA (1997a) published a public health goal (PHG) of 2 µg/L in drinking water, based on a "level of concern" of 28.6 µg/day, an uncertainty factor of 3, and a relative source contribution of 0.2 for water. The level of concern is based on CDC's Pb_B benchmark of 10 µg/dl and a Pb_B/intake slope of 0.35 µg/dl per µg/day. The uncertainty factor is to account for uncertainty regarding the protectiveness of the level of concern. OEHHA (1997) also established a No-Significant-Risk Level of 15 µg/day based on carcinogenic effects and a Maximum Allowable Dose Level of 0.5 µg/day for reproductive effects. The documents are available at: http://www.oehha.ca.gov/prop65/pdf/June2004StatusRpt.pdf.

The U.S. Environmental Protection Agency has not developed a reference dose (RfD) or reference concentration (RfC) for lead (http://www.epa.gov/iris/subst/0277.htm). The National Ambient Air Quality Standard for Pb is 1.5 µg/m^3 (http://epa.gov/air/criteria.html).

General Toxicology

The database for lead contains abundant human toxicology information that is the basis for most lead health criteria, with laboratory animal data serving in a supporting role. The exposure component of the database is usually expressed in terms of lead concentration in the blood [usually reported in micrograms per deciliter (µg/dl)], teeth, or skeleton. These data do not distinguish between lead concentrations that result from exposure to organic versus inorganic lead. Although having a measure of internal dose is certainly advantageous, a single Pb_B measurement is a momentary indicator of lead in one compartment of a dynamic system. Lead in blood may be recently absorbed from environmental sources or it may represent lead that is being resorbed from the skeleton (the principal depot for lead in the body) and other body depots.

Lead can affect the cardiovascular, gastrointestinal, hemolymphatic, urinary, immune, nervous, and reproductive systems, and can cause tumors in laboratory animals (ATSDR, 1997). Prenatal exposure to lead can cause reduced birth weight and premature births

(Bellinger et al., 1991b). This document is generally limited to the non-carcinogenic effects of lead, and is primarily focused on those effects that occur at the lowest Pb_B and those that may differentially affect children and neonates.

Prenatal or postnatal Pb exposure can adversely affect learning and behavior and may affect the endocrine and reproductive systems (California Air Resources Board, 1997). The minimum Pb_B causing neurobehavioral deficits is not well defined. As Pb_B in children and neonates continues to decline, our ability to study significant numbers of children with very low Pb_B, and therefore our ability to detect small differences in performance measures, continues to increase. Lidsky and Schneider (2003) concluded that the present 10-µg/dl upper limit on acceptable Pb_B is too high.

Neurological effects

Epidemiological studies in the 1970s and 1980s generally found maladaptive behavior, slower reaction times, decreased nerve conduction velocity, and reduced IQ scores, and reading, spelling, and mathematics performance, in pre-school and school-age children with increasing blood or tooth lead levels (Banks et al., 1997). The investigators generally examined children with Pb_B ranging from 5-9 µg/dl at the low end to 32-60 µg/dl at the high end. Tooth lead levels generally ranged from 2-9 ppm to 24-32 ppm, respectively.

Five of six cohorts followed longitudinally in the late 1980s and early 1990s exhibited significant inverse relationships between Pb_B at birth to 5 years of age and one or more measures of linguistic ability, visual-spatial relations, sensory-motor co-ordination, memory, motor skills, verbal, perceptual, or quantitative skills, or various measures of achievement (Banks et al, 1997). Children in these cohorts generally had Pb_B ranging from 1-8 µg/dl at the low end to 15 to 35 µg/dl at the high end. In most cases, postnatal exposure had a stronger effect on outcomes than prenatal exposure. Some of these studies showed more pronounced effects of lead in lower socio-economic status (SES) children and/or in boys. None of the studies concluded that lead was the most important influence on cognitive development.

Several more recent reports indicate that the effect of lead on cognitive abilities extends to Pb_B levels below 10 µg/dl, the concentration that has served as the "bright-line" for risk management for more than a decade. Schwartz (1994) analyzed data from eight longitudinal and cross-sectional studies of IQ published between 1981 and 1992 involving a total of 7700 school-age children. Mean Pb_B for children in these studies ranged from 6.5 to 21 µg/dl. A meta-analysis of these data resulted in a composite IQ/Pb_B slope of -0.26 ($\pm$0.04) IQ points per µg/dl. There was an apparent increase in slope with decreasing Pb_B. Schwartz concluded that the association between Pb_B and IQ continues at Pb_B below 5 µg/dl.

Lanphear et al. (2000) assessed the relationship between Pb_B and age-adjusted performance on tests of arithmetic and reading skills, nonverbal reasoning, and short-term memory among 4853 children ranging from 6 to 16 years of age using data from the Third National Health and Nutrition Examination Survey (NHANES III**;** available at http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm). Gender, race, poverty index, educational level of caregiver, serum ferritin and cotinine levels, tobacco-smoke exposure, and birth weight were all related to Pb_B. These variables, along with region of country, marital status of the head of household, and use of neonatal intensive care, were included as potential covariates in a multiple regression analysis relating Pb_B to performance on the four tests. The adjusted slopes for five Pb_B groupings are shown in Table 1. All regression

coefficients were negative for all four tests; those shown in bold were statistically significant. The authors suggest that their results, along with the results of other studies, suggest that the "acceptable" blood lead should be ≤5 µg/dl.

Table 1: Adjusted Slopes of Composite Performance Scores versus Pb_B

Test	Block Design[1]		Digit Span[1]		Arithmetic[2]		Reading[2]	
Pb_B	Slope	P	Slope	P	Slope	P	Slope	P
All	**-0.1**	.009	**-0.05**	0.04	**-0.7**	<0.001	**-0.99**	<0.001
<10 µg/dl	**-0.13**	0.03	**-0.08**	0.03	**-0.89**	<0.008	**-1.44**	<0.001
<7.5 µg/dl	**-0.11**	0.04	-0.09	0.11	**-1.06**	0.01	**-1.53**	<0.001
<5.0 µg/dl	-0.05	0.45	-0.09	0.2	**-1.06**	0.03	**-1.56**	<0.001
<2.5 µg/dl	-0.08	0.72	-0.25	0.17	-1.28	0.2	-1.71	0.07

[1] Standardized to a mean score of 10
[2] Standardized to a mean score of 100

Stone and Reynolds (2003) critiqued this work, citing shortcomings in the NHANES III data, including potential inaccuracies in data collection, missing data, "odd distributions" of Pb_B data and cognitive and academic scores, and failure to include potentially important covariates. They question the representativeness of the sub-sample analyzed, judging it not applicable to the general population because of bias toward low SES. While this would be a concern if we were attempting to extrapolate the results to the entire U.S. population, it does not affect this application, since the BC_B must protect sensitive subgroups. Their concerns do not negate the overall conclusions of Lanphear et al. (2000) that lead affects cognition in at least some segments of the population at Pb_B well below 10 µg/dL.

Wang et al. (2002) studied class rankings in 934 children in Taiwan with a mean age of 8.85 years and Pb_B levels ranging from 0.2 to 25.5 µg/dl (12 children exceeded 10 µg/dL Pb_B and one exceeded 15 µg/dL). Class rankings in Chinese, Mathematics, Natural Science, and History and Society were all inversely associated with Pb_B ($p<0.01$). In a multiple regression analysis, the fathers' socioeconomic status and the mothers' education were found to be significant predictors of the child's achievement. After adjusting for these factors, concurrent Pb_B was still a significant predictor of class rankings ($p<0.05$). These three variables explained five to 14 percent of the overall variance in class rankings in the four areas of study. These relationships remained significant at Pb_B below 10 µg/dL.

Canfield et al. (2003a) studied the relationship between Pb_B at 6, 12, 18, 24, 36, 48, and 60 months of age and the composite scores of 172 children on the Stanford-Binet Intelligence Scale at the ages of 3 and 5 years. The authors included sex, birth weight, serum transferrin saturation, the mother's IQ, years of education, race, tobacco use during pregnancy, household income, and Home Observation for Measurement of the Environment Inventory (HOME) score as fixed classification factors or covariates. Each of these variables except transferrin saturation was apparently related to Pb_B and to composite Stanford-Binet scores.

After adjustment for the above nine covariates, Pb_B was significantly inversely related to IQ score, with no significant difference between the 3- and 5-year evaluations. Linear regression analysis predicted a reduction of 0.46 IQ points for each µg/dl increase in Pb_B (95% CI = -0.15 to -0.76). For the 101 children whose peak Pb_B was less than 10 µg/dl, the slope was -1.37 IQ point per µg/dl Pb_B (95% CI = -0.17 to -2.56). Finally, a polynomial model fit to the data for the full sample of children predicted a 7.4-point decline (95% C.I. = -3.2 to -12.9) in IQ corresponding to an increase in Pb_B from 1 to 10 µg/dl. These results generally corroborate the results of Lanphear et al. (2000), and support the view that adverse effects are associated with Pb_B below the current 10 µg/dl CDC level of concern.

Bellinger et al. (1987) studied 249 infants using the adjusted Mental Development Index of the Bayley Scales of Infant Development (MDIA) administered at 6, 12, 18, and 24 months of age. From a cohort of ~2500 infants born between April and July 1979, 85 were selected to represent <10th percentile exposure (umbilical cord Pb_B<3, mean 1.8$\pm$0.6), 88 to represent ~50th percentile exposure (cord Pb_B 6-7 µg/dl, mean 6.5$\pm$0.3), and 76 to represent >90th percentile exposure (>10 µg/dl, mean 14.6$\pm$3.0). Although the low umbilical cord Pb_B group remained lowest in Pb_B at 6, 12, 18, and 24 months, the separation between the medium and high groups was not maintained. After adjustment for 12 potential confounding variables, the children's rankings on MDIA scores were opposite to their rankings in cord blood Pb levels (i.e. higher Pb_B was associated with reduced development). The F statistic was significant at 12, 18, and 24 months ($p<0.05$) but not at 6 months ($p=0.095$). Actual MDIA scores were compared with expected scores based on 12 predictors of mental development, and the difference expressed as a deficit compared with expected values (Table 2).

Table 2 Mental Development Index scores versus Umbilical Cord Pb_B

Umbilical Cord Pb_B	Mental Development Index scores (observed-expected)			
	6 months	12 months	18 months	24 months
<3 µg/dl, mean 1.8$\pm$0.6	1.72 ± 1.20	1.46 ± 1.46	2.12 ± 1.75	2.28 ± 1.58
6-7 µg/dl, mean 6.5$\pm$0.3	-0.06 ± 1.25	1.60 ± 1.38	1.22 ± 1.76	1.82 ± 1.60
>10 µg/dl, mean 14.6$\pm$3	-1.90 ± 1.20	-3.54 ± 1.54	-3.81 ± 1.97	-4.38 ± 1.76

Bellinger et al. (1991) assessed 169 of the original 249 children again at 57 months of age using Pb_B at 6, 12, 18, 24, and 57 months, and integrated Pb_B over various age spans as the independent variable and General Cognitive Index of the McCarthy Scales of Children's Abilities (GCI) scores as the dependent variable. GCI is a composite score combining results on the verbal, perceptual-performance, quantitative, memory, and motor subscales. After adjustment for 13 potential confounding variables using a multiple regression model, GCI scores were inversely related to Pb_B, but the coefficient was statistically significant only for Pb_B at 24 months. When the children were grouped according to their Pb_B at birth, and at 6, 12, 18, 24, and 57 months of age (low: <3 µg/dl, medium: 3 – 9.9 µg/dl, and high: >10 µg/dl, GCI scores in the groups with low concurrent Pb_B exceeded the scores of the children in the medium Pb_B group at the corresponding ages by 3.0 to 5.3 points.

Several studies have yielded results that suggest interactions between Pb_B and other variables e.g. SES (Schneider, et al. 2001). Children of lower SES were more affected by increased Pb_B than were children of higher SES (Bellinger, 2000). This so-called protective effect of higher SES did not extend to children with the highest Pb_B.

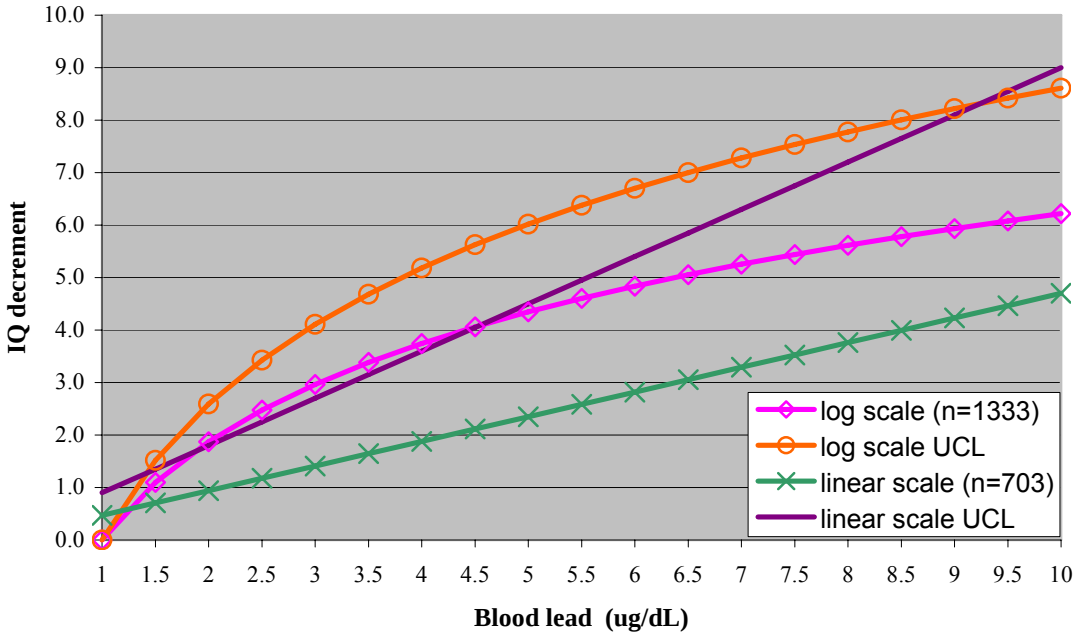
To evaluate the association between body lead burden and social adjustment, 850 first-grade boys in a public school who scored in the upper 30 percent of the distribution on a self-reported antisocial behavior scale were matched with an equal number drawn by lot from the lower 70 percent of the distribution. From this sample, 301 students accepted the invitation to participate. Lead exposure was estimated using x-ray fluorescence spectroscopy of subjects' tibias at age 12 years. Child Behavior Checklist (CBCL), teachers' and parents' reports, and subjects' self-report of antisocial behavior and delinquency at 7 and 11 years of age were the measures of effect. At 7 years of age, lead levels were marginally associated with the teachers' aggression, delinquency, and externalizing scores after adjustment for covariates. At 11 years of age, parent- and teacher-reported somatic complaints, delinquent, aggressive, internalizing, and externalizing behavior, along with teacher-reported attention problems, social problems, and anxious/depressed behavior, were significantly associated with lead burden. High-lead subjects scored higher in self-reported delinquency at 11 years and had an increased risk of exceeding the clinical score ($T > 70$) for attention, aggression, and delinquency. The authors concluded that lead exposure is a risk factor for antisocial and delinquent behavior (Needleman et al., 1996).

Using the Fagan Test of Infant Intelligence (FTII), Emory et al. (2003) studied memory and cognitive functioning in 79 seven-month-old African-American infants in relation to their *in utero* Pb exposure, which ranged from 0.05 to 3.3 μg/dl. Infants with FTII novelty scores in the top five percent had a mean maternal Pb_B of 0.28 μg/dl, while those in the bottom five percent had a significantly higher mean maternal Pb_B of 1.18 μg/dl. Similarly, those in the top 15 percent had a mean maternal Pb_B of 0.44 μg/dl, while those in the bottom 15 percent had a mean maternal Pb_B of 0.94 μg/dl. All upper quartile maternal Pb_B infants were in the low FTII group and vice versa (chi-square $P<0.004$). The high and low maternal Pb_B groups did not differ significantly with respect to age at testing, gestational age, birth weight, or maternal education. These results suggest that there may be cognitive differences between 7-month-old infants with maternal Pb_B around 1 μg/dl and those with maternal Pb_B around 0.25 to 0.5 μg/dl.

Lanphear et al (2005) analyzed Pb_B and full-scale IQ data from 1,333 participants in seven international population-based longitudinal cohort studies. The children ranged in age at testing from 58 months to 10 years. The children were administered a version of the Wechsler Intelligence Scales for Children-Revised, Wechsler Intelligence Scales for Children-III, Wechsler Preschool and Primary Scales of Intelligence, or Wechsler Intelligence Scales for Children-Spanish version under uniform conditions within each study. Exposure measures included concurrent Pb_B, lifetime average Pb_B, maximum Pb_B at any time prior to testing, and mean Pb_B from 6 to 24 months. Concurrent Pb_B was found to be most strongly related to IQ, and was used as the exposure metric in all subsequent analyses. Cord Pb_B data were available for some of the subjects. Of the 11 potential confounders included as covariates in the multivariate analysis, six terms significantly affected IQ: HOME score, birth weight, log of concurrent Pb_B, study site, and maternal IQ and education. Six additional terms (sex, birth order, maternal age and marital status, prenatal smoking and alcohol use) each

resulted in less than a five percent change in the coefficient and were not used in the final model. After adjustment for the five covariates that significantly affected IQ, a log-linear model: $\Delta IQ = \ln Pb_B * -2.7$ (95% CI, -3.74 to –1.66) fit the data well. This model (depicted by the curved lines in figure 1) predicted a decline in IQ of 6.9 points (95% CI = 4.2-9.4) as Pb_B increased from 2.4 to 30 µg/dl (the 5th and 95th percentiles, respectively). The model predicted a steeper decline in IQ of 3.9 points (95% CI = 2.4-5.3) as Pb_B increased from 2.4 to 10 µg/dl, while at higher Pb_B the declines were less: 1.9 (95% CI, 1.2-2.6), for 10-20 µg/dL; and 1.1 (95% CI, 0.7-1.5), for 20-30 µg/dL. The average linearized slopes over these ranges are shown in Table 4. Figure 4 in Lanphear et al (2005) suggests that a linear increase in either maximum or concurrent blood lead concentration associated with the mean change in IQ score could be estimated within the lower range of lead burden (i.e. < 10 µg/dl). One of the co-authors (Hornung, 2005) fit a linear model to the Pb_B and IQ data for 703 children with concurrent Pb_B <10 µg/dL. That additional model (depicted by the straight lines in Figure 1) estimates a slope of –0.47 with a $UCL_{97.5}$ of –0.9 That slope is compared with the other six-term linear models that were fit to data from children with lower burdens of lead in Table 4:

Figure 1: IQ decrement as a Function of Blood Pb



When scores on the verbal and performance Wechsler scales were examined separately, the performance IQ coefficient on log Pb_B was very similar to the full-scale IQ (-2.73 versus 2.70) while the verbal scale showed a slightly lower slope (2.07), using the same 5 covariates. After adjusting for concurrent Pb_B, cord Pb_B did not significantly influence IQ (p=0.21). Conversely, even with cord Pb_B included as a covariate, concurrent Pb_B was still significantly associated with IQ (p=0.019).

Non-neurological effects

Although neurological effects are the best-studied effects of lead, other systems are also affected. Fels et al. (1998) found significant increases in abnormal values in various indicators of glomerular and proximal and distal renal tubular function in 62 (exposed) ten-year-old children living near lead-producing factories compared with 50 (control) children living in the same province away from sources of environmental lead. At the time of the study, Pb_B in the controls averaged 3.9 µg/dl while exposed children averaged 13.3 µg/dl. Some of the exposed children had previously had Pb_B up to 21 µg/dl.

Wu et al. (2003) used NHANES III data self-reported attainment of menarche and physician-determined Tanner stage 2 pubic hair and breast development as indicators of sexual development in 8-16 year-old girls. After adjustment for age, race/ethnicity, income index, urban versus non-urban residence, family size, and body mass index, girls with Pb_B in the range of 2.1 to 4.9 µg/dl were 48 percent as likely (95% C.I. = 25-92%) to have attained stage 2 development of pubic hair as girls with Pb_B in the range of 0.7 to 2.0 µg/dl. They were 42 percent as likely (95% C.I. = 18-97%) to have attained menarche. Breast development was not significantly different between the groups (95% C.I. = 51-285%). Delayed sexual maturation was also seen in girls with Pb_B in the range of 5.0 to 21.7 µg/dl.

Selevan et al. (2003) studied sexual maturation in girls based on NHANES III data. Of 2741 girls aged 8-18 years, data on Pb_B and at least one measure of pubertal development were available for 2186. Ethnic breakdown included 600 white, 805 African-American, 781 Mexican-American, and 113 belonging to other racial or ethnic groups. The latter were not analyzed due to low numbers. Height, weight, and body mass index were included as covariates. As in the Wu et al. study, trained clinicians without knowledge of the girls' Pb_B status evaluated the Tanner stage of development. The age at menarche for girls 8-16 was obtained by interviewing the girls or a responsible adult. Ordinal logistic regression was used to estimate the mean age for attainment of each Tanner stage by Pb_B groups, after controlling for age, smoking, anemia, dietary calcium, iron, vitamin C, and total fat, rural versus urban residence, and family income. Geometric mean Pb_B was <3 µg/dl for all 3 racial groups, with 99.7 percent of white girls, 98.4 percent of African-American girls, and 97.7 percent of Mexican-American girls having Pb_B <10µg/dl. Results are summarized in Table 3.

Table 3: Odds ratio for girls with Pb_B = 3 µg/dl compared with girls with Pb_B = 1 µg/dl[1]

	Non-Hispanic White	African-American	Mexican-American
Breast development	0.82 (0.47-1.42)[2]	0.64 (0.42-0.97)	0.76 (0.63-0.91)
Pubic hair	0.75 (0.37-1.51)	0.62 (0.41-0.96)	0.70 (0.54-0.91)
Age at menarche	0.74 (0.55-1.002)	0.78 (0.63-0.98)	0.90 (0.73-1.11)

[1] Relative likelihood of having attained the indicator at the time of examination, fully age-adjusted
[2] (95% confidence interval) confidence intervals that do not include 1 indicate statistical significance

Two of the three indicators of sexual development were significantly related to Pb_B in Mexican-American girls and all three indicators of sexual development were significantly

related to Pb_B in African-American girls. As shown by confidence intervals that include 1, non-Hispanic white girls' sexual development was not significantly related to their Pb_B. Both this study and that of Wu et al. (2003) reported that various markers of puberty were delayed in girls with Pb_B of around 3.0 to 3.5 µg/dl, compared with girls with Pb_B in the range of 0.7 to 2.0 µg/dl. These findings suggest another potential target for effects of lead at low levels in school-age children. Related changes have been observed in rats (Sant'Ana et al., 2001), (Der et al., 1974), (Grant et al., 1980), (Sokol and Berman, 1991).

Several studies in adults have shown adverse effects particularly involving the nervous, cardiovascular, and urinary systems. Using NHANES III data, Nash et al.(2003) calculated odds ratios for diastolic hypertension by Pb_B quartile in peri- and post-menopausal women. They found statistically significant associations between Pb_B and blood pressure. For example, in post-menopausal women who had not been treated for hypertension, the odds ratio for diastolic hypertension was 4.6 (95% CI = 1.1-19.2) for women in the second quartile (Pb_B = 2.1-3.0 µg/dl) compared to those in the first quartile (Pb_B = 0.5-2.0 µg/dl). This result suggests the possibility of adverse effects in adults at Pb_B similar to those in children. However, children would still be more sensitive to environmental lead, since their exposures are higher on a body weight basis and they absorb a larger fraction of the lead they ingest.

Basis for the Benchmark Concentration for Blood Lead (BC_B)

Endpoint selection

IQ was chosen as the endpoint on which to base the BC_B because it is a sensitive marker for neurodevelopmental effects of lead and it is the most widely measured neurodevelopmental endpoint, giving us many data sets to compare. Intelligence testing for children was originally developed in France in 1905, and was translated into English and modified for American culture as the Stanford-Binet Intelligence Scale in 1916. This instrument was the dominant measure of children's intelligence in the first half of the 20th century. The United States military developed a separate but related instrument to measure the intelligence of recruits during World War I. Wechsler combined these two instruments into a the Wechsler Intelligence Scale for Children (WISC) that evolved to the WISC-III for children 6-16 and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) that is now the WPPSI-R for children 3-7. The WISC-III and WPPSI-R have eclipsed the Stanford-Binet Intelligence Scale. They include six subtests in each of the Verbal and Performance subdivisions. The Full-Scale Intelligence Quotient is a complex but consistent scoring of these subtests. Both tests have been extensively validated and shown to be reliable (Kaufman and Lichtenberger, 2000).

Study selection

The Lanphear et al. (2005) pooled analysis was selected as the basis for the BC_B for lead because it reports on a sensitive endpoint (full-scale Wechsler IQ) in 1,333 children participating in seven recent longitudinal studies in four countries, using appropriate measures of exposure, and evaluating appropriate covariates. It involved a large number of pre-school to school-age children and has sufficient statistical power to define the relationship between blood lead and cognitive function within reasonably tight confidence limits.

IQ/Blood Lead Response Slope

After adjustment for five significant covariates, log-linear regression analysis predicted an average reduction of 0.25 (95% CI = 0.15-0.34) IQ points for each µg/dl increase in Pb_B over the range of 2.4 to 30 µg/dl, corresponding approximately to the 5th to 95th percentiles of Pb_B (Lanphear et al. 2005). As depicted in Figure 1, the curve is steeper at lower Pb_B: the average slope for 703 children with concurrent Pb_B <10 µg/dl was -0.47 (95% CI = -0.04 to -0.90) IQ points per µg/dl (Hornung, 2005). The $UCL_{97.5}$ (the upper end of the 95% CI) on that slope (-0.9 points per µg/dl) is the basis for the BC_B. OEHHA chose a model based on children in the lower half of the distribution because as population-wide Pb_B levels continue to decline, more and more children will fall into this range. Also, OEHHA's mandate is to protect sensitive children, and these data suggest that children at the lower end of the exposure spectrum sensitive may exhibit a greater change in IQ for a given change in Pb_B. In order to be reasonably certain that the result is not an underestimate of the true slope, the 97.5 percent upper confidence limit on the slope was used to account for variability and uncertainty in the data. Alternative choices and the effects of those choices are discussed below.

Benchmark Response

To be a public health concern, a change must be both adverse and significant. OEHHA considers cognitive deficits to be adverse. Therefore, the selection of a threshold for regulatory concern depends on significance, by which we mean that it is reproducible and not due to chance alone. Based on review of several published reports, OEHHA is confident that Pb_B levels above 1 µg/dl do adversely affect cognitive function. However, Pb_B and cognitive function are not frequently reported as fractional µg/dl and IQ points, respectively. Thus data relating Pb_B at levels below 1 µg/dl to changes in IQ are somewhat speculative, and too uncertain to use as the basis for establishing a BC_B.

U.S. EPA's Web site describes several approaches to setting a benchmark response rate for continuous variables at: (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167). EPA (2000) recommends that regardless of what benchmark is actually used, the response rate equal to one control standard deviation be given. For IQ, one control standard deviation is 15 points, since the distribution of IQ in the population is designed to be normal with a mean of 100 and a standard deviation of 15.

The BC_B calculation was as follows:

$$BC_B = \frac{-1\ I.Q.\ \text{point}}{-0.90\ I.Q.\ \text{points}\ \ per\ \mu g/dl * (UF = 1)} = 1.1\ \mu g/dl\ Pb_B$$, rounded to 1 µg/dl

An uncertainty factor (UF) of one is proposed because there is no interspecies or intraspecies extrapolation, since the data are based on sensitive humans, and the database was not considered deficient.

Comparison of Alternative Choices

In developing this BC_B, several choices had to be made, including which endpoint and study to use, which model from that study, which portion of the curve, and what level of

predicted impairment to allow. Alternative choices and the effects of those choices are discussed below and summarized in Table 4.

Intellectual function as measured by full-scale Wechsler IQ was chosen as the relevant toxicological indicator because it is the best-studied marker of neurodevelopmental effects and it is directly relevant to infants and school children. A point at which the dose-response curve flattens out – i.e. where further reductions in Pb_B yield no further improvement in intellectual functioning – has not been identified. Therefore a minimally significant change rather than a no-observable-adverse-effect-level was used. For the benchmark response, OEHHA chose a decrement of 1 IQ point (0.067 standard deviations). Since the shape of the dose/response curve below the observable range is unknown, extrapolation beyond the observable range is not considered prudent. A no-adverse effect level (NOAEL) to support a NOAEL/UF approach was not identified.

Table 4: Results of Alternative Choices

Reference	Indicator	Slope	BC_B[1]	UCL[2]	BC_B[1]
Lanphear et al., 2005	Log-linear all children	-0.69	1.4	-0.96	1.0
	Log-linear, slope from 2.4 to 30 µg/dl	-0.25	4.0	-0.34	2.9
	Log-linear, slope from 2.4 to 10 µg/dl	-0.51	2.0	-0.70	1.4
	Linear concurrent Pb_B <10 µg/dl	-0.47	2.1	**-0.90**	**1.1**
	Linear maximum Pb_B <10 µg/dl	-0.74	1.4	-1.74	0.6
	Linear maximum Pb_B <7.5 µg/dl	-2.94	0.3	-5.16	0.2
Canfield et al., 2003	Polynomial	-0.82	1.2	-1.43	0.7
	Linear: children w/ Pb_B <10	-1.37	0.7	-2.56	0.4
	Linear: all children	-0.46	2.2	-0.76	1.3
Schwartz, 1994	Aggregate from 8 studies	-0.26	3.8		
Lanphear et al., 2000	Arithmetic	-0.89	1.1		
	Verbal	-1.44	0.7		
	Block design	-1.30	0.8		
	Digit span	-0.80	1.3		
Benchmark IQ decrement		5.0 pts	5.0		
		1.5 pts	1.7		
		1.0 pt	**1.1**		

[1]Effect of this choice assuming that all other choices remain as recommended
[2] The upper end of a 95% confidence interval is the same as a 97.5% UCL

Lanphear et al. (2005) reported that the relationship between Pb_B and IQ was non-linear, with significant quadratic and cubic terms, after adjustment for five significant covariates. A log-linear function fit the data well. However, it would be impractical to use the actual log-linear slope as the basis for the BC_B. Since the slope of such a curve is different at every point on the curve, the user would have to know the pre-existing Pb_B of each child in order to calculate a benchmark dose for that child, assuming the same incremental decrease in IQ due to lead exposure at school was to be allowed in each child. In order to avoid that unworkable outcome, OEHHA identified two potential approaches: 1) calculate the average change in

Pb_B over some range based on the log-linear function, or 2) the chosen linear model (-0.47 (95% CI = -0.04 to -0.90) IQ points per µg/dl, Hornung, 2005), based on children with Pb_B up to 10 µg/dl. Choosing either of these 2 approaches would have resulted in a BC_B that was the same expressed to one significant figure.

OEHHA, (1997b) used a slope of -0.33 points of full-scale IQ for each 1 µg/dl increase in Pb_B in children over 5 years of age. The slope that is proposed as the basis for the BC_B is about three times the earlier slope. It is based on newer data, which have shown a slightly greater effect than earlier studies, particular at the lower end of the Pb_B range. The chosen slope will probably overestimate the effect of a given change in Pb_B among children with higher Pb_B.

Cumulative Exposure

Table 5 shows predicted incremental Pb_B increases and corresponding IQ decrements related to various environmental sources in addition to those associated with the school site. These additional sources should be considered in the development of risk management strategies. Drinking water samples from 200 randomly selected schools between 1995 and 1997 showed that 18 percent had lead concentrations exceeding the federal standard of 15 µg/L (http://www.dhs.ca.gov/childlead/schools/execsum.htm).

Table 5: Other Sources of Lead Exposure

Medium	Pb concentration	Corresponding increase in Pb_B (99^{th} percentile)[1]	Upper bound IQ decrement
Air[2]	0.028 µg/m^3	0.11 µg/dl	0.1
Water[3]	15 µg/L	2.9 µg/dl	2.7
Food[4]	3.07 µg/kg	1.6 µg/dl	1.4
Candy[5]	0.1 µg/g	1.6 µg/dl	1.4

[1] Based on the Leadspread model with default background levels of lead in environmental media
[2] The highest monthly average atmospheric concentrations measured by CARB in 1997
[3] Based on the federal action level. Most California water supplies are well below this level
[4] Based on FDA Total Diet Study (1999). Dietary concentrations in 2005 are probably lower.
[5] Based on 100 grams daily consumption

Using the BC_B

The BC_B presented herein was developed for use in the California Environmental Protection Agency school site evaluation programs. It differs from a typical chRD or chRC in two respects: a) it represents a concentration in a body fluid rather than a concentration in an exposure medium like air or water, and b) it is an incremental increase in Pb_B that would be associated with a marginally detectable change in IQ in a population, rather than a daily exposure that is below a level that might cause an adverse health effect. Since many children have Pb_B exceeding 1 µg/dl before any exposures occurring at school, the BC_B is intended to be used as a *de minimus* increase in Pb_B resulting from exposure to environmental lead.

There are several models to calculate the increase in Pb_B resulting from environmental lead exposures. OEHHA (2004) suggests using the California Department of Toxic

Substances Control's Lead Risk Assessment Spreadsheet (available at http://www.dtsc.ca.gov/AssessingRisk/leadspread.cfm). Using this model, one could employ the "goal seek" function in Excel® to calculate the increase in soil Pb that would result in a predicted 1 µg/dl increase in Pb_B for appropriate population percentiles.

The BC_B is intended to apply to pre-school infants and children, to students through high school, and to school staff. While there is no well-established age limit for lead's neurodevelopmental effects, sexual maturity and the possibility of pregnancy begin at an age close to the probable upper end of the age range for neurodevelopmental effects. Chen et al. (2005) have shown that concurrent Pb_B in seven-year-olds continues to affect IQ beyond the effects of early exposure. Bellinger et al. (1992) found a measurable relationship between Pb_B at five years of age and IQ at 10 years of age.

Discussion

Association versus Causality

The existence of a relationship between Pb_B and various neurobehavioral indicators is well established in humans. Yet the nature of that relationship has been debated for decades. Many factors influence the intellectual abilities of children, including the IQ and socio-economic status (SES) of their parents and the quality and stability of the home environment (Wasserman, 2001, Nation, 2001). These and other determinants of intellectual development are often correlated with blood lead levels, creating a challenge to separate the effect of lead from the effects of the other variables. Although there is no doubt that socio-demographic factors affect intellectual development directly, they may also affect exposure to lead, thereby confounding the association between lead exposure and neurological effects. If two or more independent variables (risk factors) are strongly correlated, it is difficult to know how much of the variation in the dependent variable (intellectual abilities) to allocate to each of the various risk factors, i.e., which of the relationships depicted in the diagrams below is correct (Needleman, 2001). If the incorrect relationship is inferred, then adjusting for covariates may result in the misattribution of the effects of Pb_B to other factors that are correlated with Pb_B. Recent studies have employed multiple regression analysis to allocate the variation in intellectual abilities among the various risk factors (Canfield et al., 2003b). This method has shown many parental and socio-economic factors to be strongly related to blood lead and to intellectual abilities. However, in most cases, adding blood lead as an independent variable into a regression equation adds significant predictive ability to the equation. This result would not be expected if lead did not play an independent role in determining the intellectual abilities of children (Wasserman, 2001). Multiple regression analysis may or may not accurately allocate variation in intellectual ability, since among strongly correlated risk factors, one factor may be substituted for another with minimal impact on the goodness of fit. However, the fact that there are several risk factors for diminished intellectual capacity, some of which may be quantitatively more important, does not alter our mandate to protect school children from the effects of toxic chemicals. For our purposes, it is sufficient to show that low Pb_B concentrations play a direct role in the etiology of diminished intellectual capacity in affected children. Several possible causal relationships are consistent with the observed correlations among neurobehavioral indicators, Pb_B, and SES and other potential risk factors. Figure 2 depicts these possibilities.

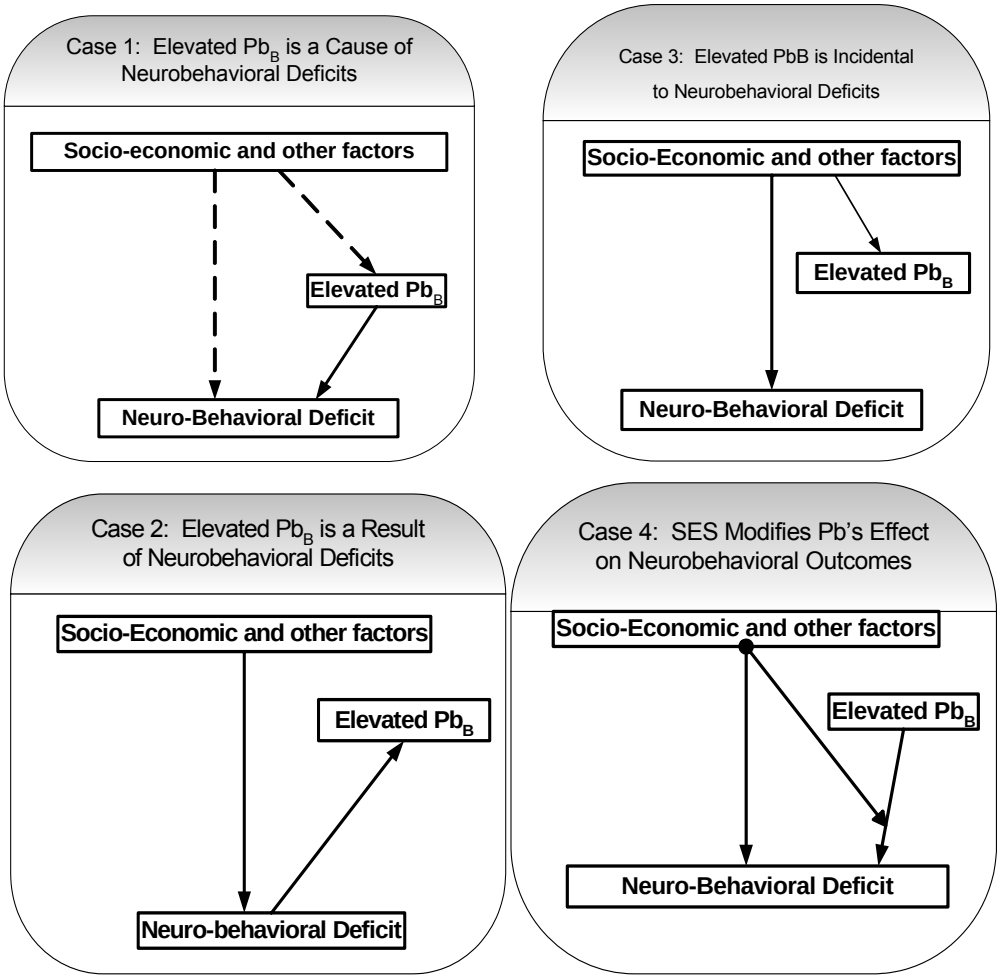


Figure 2: Postulated explanations for the observed correlations between neurobehavioral indicators, Pb_B, and SES and other potential risk factors. **Case 1:** Lead interferes with some aspect(s) of CNS functioning leading to neurobehavioral deficits. As indicated by the dashed arrows, lead may be an intermediate on the pathway from SES or other factors to intellectual deficits, and/or it may be one of multiple causes. **Case 2:** The altered behavior of neurologically challenged infants and children somehow increases their exposure to environmental lead (so-called "reverse causality"). **Case 3:** SES or other factors are confounders of the effect of lead exposure on neurobehavioral deficits. PbB is not causally related to lowered intellectual functioning, but is independently linked to a third factor or group of factors (e.g. SES), which is causally related to lowered intellectual functioning. **Case 4:** Lead interferes with some aspect(s) of CNS functioning leading to neurobehavioral deficits, and SES or other factors modify this effect.

One approach to sorting out these relationships is to study populations in which the factors under study are not correlated in the usual way. Factor-Litvak et al. (1999) conducted a prospective study comparing Yugoslavian children living near a smelter with a control group of similar age and parental education. This cohort was unusual in exhibiting a slight positive correlation between Pb_B and socio-economic status, in contrast to the more typical inverse relationship. Significant associations were found between Pb_B and height at 4 years and several behavioral problems at 3 years of age. Changes in cognitive indices associated with an increase in concurrent blood lead from 10 to 30 µg/dl are shown in Table 6. As indicated by the fact that the confidence intervals do not include zero, all adjusted slopes were significant at the 0.05 level. All slopes increased after adjustment for HOME score, ethnic group, maternal age, birth weight, maternal Raven's progressive index, maternal education,

birth order or number of siblings, and hemoglobin levels (ages 2 and 4 only). This is important, because it indicates that in the unadjusted ratios the effect of lead was being partly offset by differences in these other variables, which were inversely related to lead. After adjustment, the effect of lead became stronger, supporting the position that it is the lead that is causing the deficit, not some other variable that is correlated with lead exposure.

Table 6: Changes in Cognitive Indices Associated with an Increase in Pb_B from 10 to 30 µg/dl

Endpoint		Unadjusted change	Adjusted[1] change	
			Mean	Confidence interval
Bayley Mental Development Index (age 2)		-3.3	-5.3	-0.5 to -10.1
McCarthy Scales (age 4)	General Cognitive Index	-7.1	-9.4	-4.6 to -14.2
	Perceptual	-6.6	-7.1	-3.9 to -10.2
	Verbal	-0.8	-2.7	-0.1 to -5.4
	Quantitative	-5.5	-5.9	-2.3 to -9.6
	Memory	-1.0	-3.2	-0.5 to -5.8
	Motor	-2.6	-4.3	-0.3 to -8.3
Wechsler Scales (age 7)	Full Scale IQ[1]	-4.7	-9.0	-5.5 to -12.4
	Performance IQ[1]	-4.5	-9.4	-5.6 to -13.3
	Verbal IQ[1]	-3.7	-7.1	-3.7 to -10.5

[1] The six Verbal Scale tests use language-based items; the seven Performance Scales use visual-motor items that are less dependent on language. Five of the subtests in each scale produce scale-specific IQs, and the 10 subtest scores produce a Full Scale IQ

Neonatal behavioral evaluations can limit the influence of the post-natal environment on study outcomes, thereby helping to clarify the relationship between independent and dependent variables. Emory et al. (1999) examined 103 clinically healthy 1-2 day-old African-American infants using the Brazelton Neonatal Assessment Scale administered by trained examiners blinded to maternal Pb_B levels in the sixth and seventh gestational months, which were generally <10 µg/dl. Correlation and dose-effect trends reveal slightly poorer attention and motor control performance among offspring of mothers with higher Pb_B. When infants were divided into approximate terciles (Pb_B <1.1, 1.2 – 1.7, and >1.8 µg/dl), significant trends were found in Brazelton Scale scores on individual items relating to motor activity. Analysis of Variance (ANOVA) F-test one-tailed P values were <0.01 for both hand-to-mouth facility and general tonus. Post hoc analysis demonstrated significant differences between the first tercile and the second and third terciles. These differences could not be attributed to birth weight or gestational age. Other variables, relating to autonomic sensitivity or emotional responses, were not significantly different between Pb_B groups. Although it is theoretically possible that heritable factors influenced the maternal Pb_B levels and the observed developmental differences, the homogeneity of this study group makes it

unlikely that SES, race, and demographic factors would be sufficient to explain the association between lead and neurological development.

Additional evidence from studies in other species

In addition to the extensive studies of lead exposure in children, controlled laboratory animal studies can help clarify the role of various variables in neurobehavioral outcomes because it is possible to limit the variables to the one under study, i.e. lead. Positive results under such conditions would argue against the "reverse causality" or "incidental co-variation" hypotheses. Primates are particularly valuable as research subjects because they can be given learning tasks that are similar to those given to children. The experimental evidence for causal effects of lead on neurobehavioral development supports the epidemiological evidence. Several examples are given in the following paragraphs.

Monkeys dosed with lead from birth reached blood levels of 115 µg/dl in infancy, then leveled off to 35 µg/dl by a year of age. Despite the high Pb_B, the monkeys did not show signs of overt toxicosis, nor any increase in overall locomotor activity. Treated monkeys learned tasks more slowly than controls and responses to a fixed reinforcement schedule were less stable. Monkeys treated only during infancy or only after infancy showed similar results when tested at ages 3 and 7-8 years (Banks et al., 1997).

Rats dosed with lead to reach blood levels of 19 or 39 µg/dl showed impairment in serial reversal learning and fixed-interval responding tasks, and delayed spatial alternation, findings similar to those reported in monkeys (Banks et al., 1997).

Morgan et al. (2001) exposed rats to lead during gestation and lactation or during lactation alone to produce maximum Pb_B on postnatal day 24 of 158 µg/dl, declining to 12-16 µg/dl on postnatal day 53. This treatment regimen caused impaired sustained attention and increased reactivity to errors, when cue duration and cue onset varied unpredictably between trials. The authors suggest that these changes may be related to the disruptive classroom behavior, low IQ scores and delinquency observed in lead-exposed children. Other investigators have shown hyperactivity, decreased exploratory behavior, and impairment of learning and memory in rats exposed during gestation and lactation with Pb_B of 21 ± 3 µg/dl (Moreira et al., 2001).

Summary and Conclusions on Causality

Based on multiple lines of evidence, OEHHA concludes that lead is a causal factor in neuro-developmental deficits. Regression analysis of data from many epidemiologic studies has shown that lead exerts an independent effect on neurodevelopment and cognition, after adjustment for differences in other factors known to influence the same outcomes. Reverse causality is not a likely explanation, because differences can be found at birth. In one study in which Pb_B was not inversely correlated with SES, the observed effect of lead on IQ tests was increased after adjustment for differences in SES. Finally, similar effects have been seen in controlled studies in several non-human species.

Temporal Pattern of Pb-induced Neurobehavioral Deficits

To determine the temporal pattern of the effect of postnatal Pb_B on the General Cognitive Index, Schnaas et al. (2000) used the McCarthy Scales, translated into Spanish, to

test 112 children from the Mexico City Prospective Lead Study with complete evaluations from 36 to 60 months of age at 6-month intervals. They controlled for 5-min Apgar[1], birth weight, birth order, sex, socioeconomic level, maternal IQ, and maximum maternal educational level in a repeated measures analysis of variance. They used the children's Pb_B measured every 6 months, and averaged over 6-18, 24-36, and 42-54 month periods as the exposure indicator. Average Pb_B for the 6-18 and 24-36 month intervals had an increasingly negative effect on GCI results at 36 to 48 months; the effect of early Pb_B leveled off then declined after 48 months. Pb_B at 42-54 months was significantly correlated with GCI at 54 months ($p = 0.04$) and at 60 months ($p = 0.06$).

Soong et al. (1999) studied a group of 28 exposed students at a kindergarten located next to a lead-recycling plant and an otherwise similar reference group of 28 students at a pre-school 5 km away. The children who had attended the exposed preschool for 1-3 years (mean = 23 mo.) had a median Pb_B of 15.1 µg/dl. The exposed children had significantly ($p<0.001$) lower IQ scores (median = 94.5) than the reference children (median=101). The exposed students were then moved 2 km away from the recycling plant. Both groups were re-assessed two years later. During this time, the median Pb_B in the exposed and reference groups fell from 15.1 to 8.5 µg/dl and from 8.5 to 7.0 µg/dl, respectively. The follow-up median IQ scores were 107 and, 109.5 respectively. The average increase was significant in the exposed group, but not in the reference group. These results indicate significant recovery in IQ scores as Pb_B fell by nearly 7 µg/dl.

Chen et al. (2005) studied the relationship between Pb_B at 2, 5, and 7 years as well as average and peak Pb_B on MDI or IQ scores at 2, 5, and 7 years. The 780 children were enrolled in a chelation treatment study, but the treatment group (chelator or placebo) did not significantly affect the relationship between PbB and IQ or MDI score. Each Pb_B measurement and the average up to each age was a significant predictor of all concurrent and subsequent IQ or MDI scores. In a multivariate analysis using concurrent and prior Pb_B values as independent variables, concurrent Pb_B was always more predictive than prior Pb_B. This supports the position that lead continues to be toxic in school-age children, i.e., that the damage is not purely a function of Pb_B up to 2 years of age.

To test the hypothesis that long-term behavioral changes may result from sub-chronic Pb exposure, mice were given 5, 10, or 25 mg/kg Pb acetate intragastrically on postnatal day 6, 9, 12, 15, and 18. On postnatal day 38-42, the mice were individually tested in an unbaited tunnel maze. Locomotor activity, exploration, and experience-dependent changes in cul-de-sac entries were recorded. Although Pb_Bs were below 10 µg/dl at the time of behavioral testing, exposed mice showed a dose-dependent increase in cul-de-sac entries. The results suggest that sub-chronic Pb exposure during development produced behavioral changes that lasted well beyond the exposure period, even though Pb_B declined to <l0 µg/dl (Stewart et al., 1998). Monkeys dosed with lead for their first post-natal year reached a Pb_B of 36 µg/dl. By age four, when their Pb_B was 5 µg/dl (controls were at 4 µg/dl), they were impaired in a learning reversal task, indicating lack of full recovery from the effects of lead exposure during infancy (Banks et al., 1997).

[1] See http://www.childbirth.org/articles/apgar.html for explanation

Mechanisms of lead toxicity

Chronic lead (Pb) exposure has been associated with cognitive impairments in children and laboratory animals. Children with Pb_B in the 7 to 59 μg/dl range showed concentration-related increases in latency of brain stem auditory evoked potentials. Rats treated with lead to produce a blood concentration of 65 μg/dl showed increased latency of visual evoked potentials to visual stimuli. Similar increases were seen in lead-exposed monkeys. Spontaneous activity of cerebellar Purkinje cells is reduced in lead-treated cats and rats. This impairment persists long after tissue lead has returned to normal (Banks et al., 1997).

Studies in laboratory animals have identified some of the processes underlying the lead-induced cognitive dysfunction, including impaired synaptic plasticity and long-term potentiation (LTP). Carpenter et al. (1994) define LTP as a prolonged increase in synaptic efficacy triggered by brief tetanic stimulation at certain central synapses. Increases in LTP induction threshold, and decreases in LTP duration occurred at intermediate Pb_B (27-62 μg/dl), but not at higher exposures. The ability of Pb to diminish presynaptic transmitter release may contribute to a reduced capacity for LTP at lower exposure levels. The reversal of the effect of Pb on glutamate release at higher exposure levels may serve to compensate for the mechanism underlying the LTP impairment and form the basis for the biphasic dose-response pattern seen with chronic developmental exposure (Gilbert et al., 1999a). The LTP induction threshold was also increased in the dentate gyrus of rats chronically exposed to Pb from birth (Gilbert et al., 1999a). Changes in synaptic processes underlie the changes in LTP: Stimulated glutamate release is diminished in the hippocampus at intermediate, but not at higher, Pb_B (Lasley and Gilbert, 2000). More recently, Lasley and Gilbert (2002) showed that chronic Pb exposure produced decreases in total K^+-stimulated hippocampal glutamate and gamma-amino butyric acid release. Maximal effects were seen at a Pb_B of 40 μg/dl. Changes in total release could be traced to alterations in the Ca^{+2}-dependent component. In the absence of Ca^{+2}, K^+-induced release was elevated in the highest exposure groups, suggesting a Pb-induced enhancement in evoked release. This pattern of results is similar to that for the inhibition of LTP at similar Pb_B levels and suggests two actions of Pb on transmitter release: suppression of stimulated release at exposure levels of 27-62 μg/dl with Ca^{+2}-mimetic induction of exocytosis at exposure levels above 62 μg/dl. These findings suggest that decreases in stimulated glutamate release are a significant contributing factor to the exposure-related changes seen in LTP.

Experimental in vivo and in vitro Pb exposures produce a variety of changes in central nervous system tissues, although findings are not always consistent. Several authors have described effects on synaptogenesis in monkeys, rats, and guinea pigs due to interference with the action of neural cell adhesion molecules (NCAM) (Banks et al., 1997). The translation of neural activity into lasting synaptic change appears to involve NCAM function. Lead blocks neuroplastic events necessary for hippocampal LTP and it interferes with critical NCAM-mediated synapse selection that is critical in determining what is retained in memory. This may account for the persistent deficits in passive avoidance learning in adult rats even after cessation of Pb exposure. Adult rats previously treated with Pb from birth to postnatal day 30 learned a passive avoidance task as well as controls, but retained the learned task less time than controls. Immuno-histochemistry after the training showed that the treated rats had less hippocampal NCAM polysialylation, a marker for synaptogenesis (Murphy and Regan, 1999).

Lead appears to block post-synaptic N-methyl-D-aspartate (NMDA) receptors at concentrations in the range that affect learning in children. Since NMDA receptors are believed to be involved in LTP, this interference could explain the reduced learning ability. The NMDA receptor is important in the cognitive deficits associated with developmental Pb exposure (Guilarte and McGlothan, 1998). The Pb-induced changes in hippocampal NMDA receptor mRNA expression may lead to modifications in receptor levels or subtypes. This could alter the development of neuronal connections that require activation of NMDA receptors. Lead was localized in both hippocampal and cortical neurons (Lau et al., 2002). Cory-Slechta et al. (1997) demonstrated that Pb exposures alter MK-801 binding. MK-801 binding is a marker of NMDA function. Adult rats were less vulnerable to such effects than young rats.

Reduced synaptic neuroplasticity may contribute to cognitive deficits associated with Pb-induced toxicity. In a study to evaluate the critical developmental periods in Pb-induced impairment of LTP, rats were exposed to Pb through maternal milk and/or the drinking water over different developmental intervals. Pb exposure restricted to the lactation period appeared less disruptive to adult LTP in the dentate gyrus than continuous exposure beginning around birth or weaning. Rats exposed after weaning showed reductions in both magnitude and induction thresholds for population spike LTP relative to controls and to rats removed from Pb at weaning. However, LTP was impaired in animals exposed to Pb for as little as 30 days in the early postnatal period (Gilbert et al., 1999b).

Lead also appears to interfere with neurotransmitter release by affecting voltage-sensitive calcium channels. It can block calcium uptake by neural and neuroendocrine cells and can act as an intracellular calcium surrogate. Lead can interfere with the maturation of glial cells in monkeys and rats and appears to inhibit the synthesis of adenosine triphosphate. Substitution of lead for calcium in proteins such as protein kinase C can alter their enzymatic activity. Acute lead poisoning appears to damage capillary endothelium in the brain leading to leakage and brain swelling (Banks et al., 1997).

Reports that do not corroborate the effects in children and infants

Minder et al. (1998) studied 319 boys (from an original pool of 565) aged 9-12 who attended special education school in the Netherlands, using theory-based testing. The boys averaged 4.4 μg/dl Pb_B, with two percent exceeding 10 μg/dl. Several tests were used to measure specific aspects of information processing. A factor analysis did not implicate Pb_B as significant among factors affecting attention problems. Several crude associations appear to have been tested either by t-test or simple linear regression. Socioeconomic status and thumb-sucking/nail-biting were negatively associated with Pb_B. The boys' IQ scores were included as a confounding variable. Since IQ is often colinear with Pb_B, attributing differences in attention to IQ could mask any effect of Pb_B on the measured endpoints.

Ernhart et al. (1989) used Wechsler Preschool and Primary Scale of Intelligence (WPPSI) scores to prospectively examine the relationship between neuropsychological deficits and low-level lead exposure from before birth up to age 58 months. Most Pb_B measures were statistically significantly correlated with WPPSI scores. However, after adjustment for confounding variables, relationships of prenatal and preschool lead exposure to intellectual development were attenuated, inconsistent in direction, and not statistically significant. The authors concluded that the relationship between Pb_B and cognitive

development was largely a reflection of the dependence of each on the quality of the caretaking environment.

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Appendix: Key Findings of Selected Mechanistic Studies

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
1	Review Paper	--	Various	Pb2+ substitutes for Ca2+, & is back-transported via Ca-ATPase pump, enters cells by voltage-sensitive Ca channels	Pb can pass readily through the Blood-Brain Barrier, also enters CNS & PNS cells readily	Lidsky TI & Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 2003;126:5-19
2	Retinal Rod & Bipolar cells, in culture	0.21-21	Apoptosis of retinal Cells	Mitochondrial dysfunction due to nanomolar Pb concentrations. Ca release initiates apoptosis via Cytochrome C-caspase activation effector protein path.	Cell death resulting in retinal damage when exposed to Pb.	He L, Poblenz AT, Medrano CJ, Fox DA. Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore. J Biol Chem 2000; 275:12175-84.
3	Retinal Rod & Bipolar cells, in developing & adult rats	19-59	Apoptosis of retinal Cells	Mitochondrial dysfunction due to nanomolar Pb concentrations. Ca release initiates apoptosis via Cytochrome C-caspase activation effector protein path.	Degree of cell death was age- and dose-dependent with developing retina particularly sensitive to Pb exposure. Rods directly affected.	Fox DA, Campbell ML, & Blocker YS. Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure. Neurotoxicology 1997; 18:645-64.
4	Humans, Monkeys & Rats, Adult, in vivo	20-60	Retinal Cell Damage	Retinal Damage following low to moderate developmental exposure.	Developing retina sensitive to Pb exposure. Rods directly affected. Degree of cell death was age- and dose-dependent	Fox DA, Campbell ML, & Blocker YS. Functional alterations and apoptotic cell death in the retina following developmental or adult Pb exposure. Neurotoxicol 1997;18:645-64.
5	Human, clinical	15	Cellular energy & metabolism.	Accumulation of Pb in mitochondria, mitochondrial dysfunction, heme biosynthesis affected.	Cellular energy metabolism disrupted, disruptive effects on synaptic transmission, anemia.	Anderson AC, Pueschel SM, Linakis JG. In: Pueschel SM, Linakis jG, Anderson AC, editors. Lead poisoning in childhood. Baltimore: P.H. Brookes; 1996. P.75-96.
6	Rats, in vivo	--	Neuronal Cell Death	Decreased mitochondrial function.	Ordinary synaptic transmissions mediated by glutamate can be transformed into neuron killing excitotoxicity. May result with Pb exposure.	Beal MF, Brouillet E, Jenkins BG, Ferrante RJ, Kowall NW, Miller JM. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci 1993; 13:4181-92.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
7	Developing Rats, 0-21 days, in vivo	--	Neuronal Cell Death	Oxidative stress & direct as well as indirect lipid peroxidation leading to brain cell death.	Neuronal Death, effects on brain and CNS of Cd+2 exposure	Shukla GS, Hussain T, Chandra SV. Possible role of regional superoxide dismutase activity and lipid peroxide levels in cadmium neurotoxicity: in vivo and in vitro studies in growing rats. Life Sci 1987; 41: 2215-21.
8	Prenatal & neonatal Exp, Rats	21	Neuronal Cell Death	Oxidative stress & direct and indirect lipid peroxidation leading to brain cell death.	Neuronal Death, effects on brain and CNS.	Antonio AT, Corpas I, Leret ML. Neurochemical changes in newborn rat's brain after gestational cadmium and lead exposure. Toxicol Lett 1999; 104: 1-9.
9	Developing Rats prenatal & 0-21 days postnatal, in vivo	24-31	Neuronal Cell Death	Oxidative stress & direct as well as indirect lipid peroxidation leading to brain cell death.	Neuronal Death, effects on brain and CNS.	Villeda-Hernandez J, Barroso-Monguel R, Mendez-Armenta M, Nava-Ruiz C, Huerta-Romero T, Rios C. Enhanced brain regional lipid peroxsidation in developing rats exposed to low-level lead acetate. Brain Res Bull 2001; 55: 247-51.
10	Adult Rats, low dose, in vivo	--	Neuronal function	Affects energy metabolism in nerve endings in brain	Impaired neuronal function.	Rafalowska U, Struzynska L, Dabrowska-Bouta B, Lenkiewicz A. Is lead toxicosis a reflection of altered energy metabolism in brain synaptosomes? [Review]. Acta Neurobiol Exp (Warsz) 1996; 56: 611-7.
11	Rats	97.2	Neuronal function	creatine phosphate, creatine kinase, O_2 consumption & ATP increased in brain synaptosomes; Na-K-ATPase decreased.	Affects neuronal function in various ways, some depressive, some excitatory.	Struzynska L, Dabrowska-Bouta B, Fafalow-ska U. Acute lead toxicity and energy metabolism in rat brain synaptosomes. Acta Neurobiol Exp (Warsz) 1997; 57: 275-81.et al., 1997
12	in vitro, protein phosphatase study	100	2nd Messenger System Effects	nanomolar Pb concentrations substitute for Ca in activating calmodulin; higher concentration reduces calmodulin activity.	Affects intraneuronal regulation and second messenger activity via Ca-Calmodulin effects.	Kern M & Audesirtk G. Stimulatory and inhibitory effects of inorganic lead on calcineurin. Toxicology 2000; 150: 171-8.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
13	Rats, in vitro, hippocampal neurons	2	Intraneuronal Regulatory Mechanisms	Pb effects on calmodulin perturbs intracellular calcium homeostasis	Potentially disrupts normal cell activity.	Ferguson C, Kern M, Adudersirk G. Nanomolar concentrations of inorganic lead increase Ca2+ efflux and decrease intracellular free Ca2+ ion concentrations in cultured rat hippocampal neurons by a calmodulin-dependent mechanism. Neurotoxicology 2000; 21: 365-78.
14	Neurons, review article	--	2nd Messenger System Effects	Pb affects Protein Kinase C (PKC), premature activation in brains from immature rats. . PKC is involved in long-term potentiation	Potential action proliferation and differentiation could result in blood brain barrier defects leading to brain swelling	Bressler JP & Goldstein GW. Mechanisms of lead neurotoxicity. [Review]. Biochem Pharmacol 1991; 41: 479-84.
15	neurons, review article	--	2nd Messenger System Effects	Picomolar concentrations of Pb activate PKC when normally nanomolar concentrations of Ca would do the same.	Abnormal cell activation	Bressler J, Kim KA, Chakraborti T, Goldstein G. Molecular mechanisms of lead neurotoxicity. [Review]. Neurochem Res 1999; 24: 595-600.et al. 1999
16	Rats, in vivo	31.9	Neurotransmission	Chronic Pb exposure reduces hippocampal PKC expression.	Impairment of synaptic activity affects learning & memory.	Nihei MK, McGlothan JL, Toscano CD, Guilarte TR. Low level Pb2+ exposure affects hippocampal protein kinase Ca gene and protein expression in rats. Neurosci Lett 2001; 298: 212-6. et al., 2001
17	Rats, in vivo exp, weaning to 3 months.	578	Neurotransmitter storage & release, Synaptic Structural Effects	Synaptosomes have fewer synaptic vesicles & damaged mitochondria. Suggests a non-Pb/Ca mechanism that affects cell energy.	Neurotransmission affected by disrupting normal storage and release mechanisms.	Jablonska L, Walski M, Rafalowska U. Lead as an inductor of some morphological and functional changes in synaptosomes from rat brain Cell Mol Neurobiol 1994; 14: 701-9
18	Young Rats	--	Neurotransmission Effects, Transmitter Storage & Release	Synaptosomal Na-K ATPase increased by Pb exposure.	Neurotransmission affected by disrupting normal storage and release mechanisms.	Regunathan S & Sundaresan R. Effects of organic and inorganic lead on synaptosomal uptake, release and receptor binding of glutamate in young rats. J Neurochem 1985; 44: 1642-6.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
19	In vitro, synaptic membrane microsomes	--	Neurotransmission Effects, Transmitter Storage & Release	Ca-ATPase inhibited.	Neurotransmission affected by disrupting normal storage and release mechanisms.	Bettaiya R, Yallapraganda PR, Hall E, Rajanna S. In vitro effect of lead on Ca2+-ATPase in synaptic plasma membranes and microsomes of rat cerebral cortex and cerebellum. Ecotoxicol Environ Saf 1996; 33; 157-62.
20	Rat Synaptotagin, cell culture, in vitro		Neurotransmission Effects	Synaptotagin I, a protein localized in synaptic terminal that is important for transmitter release is disrupted, leading to defects in neurotransmitter release.		Bouton CM, Frelin LP, Forde CE, Godwin HA, Pevsner J. Synaptotagin I is a molecular target for lead. J Neurochem 2001; 76: 1724-35.
21	Young rats 21 days, in vivo	16-28	Neurotransmitter Receptors	Glutamate receptor disruption. Initial up regulation following 2 wks exp then pronounced down regulation with 8 months exposure. Also for AMPA receptors.	Unknown, may impair behavior.	McCoy L, Richfield EK, Cory-Schlecta DA. Regional decreases in alpha-[3H]amino-3-hydroxy-5-methylisoxazole-4-propionic acid ([3H]AMPA) and 6-[3H]cyano-7-nitroquinoxaline-2,3-dione ([3H]CNQX) binding in response to chronic low-level lead exposure: reversal versus potentiation by chronic dopamine agonist treatment. J Neurochem 1997; 69: 2466-76.
22	Rats, Chronic exp, parturition to adult	39-40	Neurotransmitter Receptors	Density of NMDA (N-methyl-D-aspartate) increased with exposure beginning at birth and continuing into adulthood.	Disruption in neurotransmitter function.	Lasley SM, Green MC, Gilbert ME. Rat hippocampal NMDA receptor binding as a function of chronic lead exposure level. Neurotoxicol Teratol 2001; 23: 185-9.
23	Rats, adult	37	Neurotransmitter Receptors	Hippocampal long-term potentiation is disrupted by chronic exposure.	Disruption in neurotransmitter function.	Gilbert ME, Mack CM, Lasley SM. Chronic developmental lead exposure increases the threshold for long-term potentiation in rat dentate gyrus in vivo. Brain Res 1996; 736: 118-24.
24	Mesencephalic dopamine cells, in vitro	62.5	Neurotransmitter Receptors, Dopamine system disruption	Decrease in number of D2 receptors suggests preferential vulnerability of D2 receptors to lead.	Results in cell necrosis, apoptosis, reduced dopamine uptake in remaining cells.	Scortegagna M & Hanbauer I. The effect of lead exposure and serum deprivation on mesencephalic primary cultures. Neurotoxicology 1997; 18(2) 331-9.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
25	Rat pups, postnatally via lactation from dams.	10-20	Neurotransmitter Receptors, Dopamine system disruption	20 µg/dl → D2 receptor ↓ in striatum but ↑ in nucleus accumbens. >50 µg/dl resulted in ↑ D1 receptors in striatum but ↓ in nucleus accumbens	Disruption in neurotransmitter function.	Widznowski DV, Finkelstein JN, Pokora MJ, Cory-Schlecta DA. Time course of postnatal lead-induced changes in dopamine receptors and their relationship to changes in dopamine sensitivity. Neurotoxicology 1994; 15: 853-65.
26	Cell culture	20.8	Effects on Glia	Differentiation of glial progenitors is delayed	Direct effects on CNS cells.	Deng W, McKinnon RD, Poretz RD. Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. Toxicol Appl Pharmacol 2001; 174: 235-44.
27	In Vivo	--	Effects on Glia	Glial progenitors become hypomyelinated and demyelinated	Direct effects on CNS cells.	Coria R, Berciano MT, Bercianco J, Lafarga M. Axon membrane remodeling in lead-induced demyelinating neuropathy of the rat. Brain Res 1984; 291: 369-72.
28	In vitro rat astroglia, 1' cell culture	20.8	Astroglia	Immature astroglia but not mature neurons sequester lead preferentially	Initially protects neurons from Pb exposure but may serve as reservoir for later release and result in prolonged exposure.	Lindahl LS, Bird L, legare ME, Mikeska G, Bratton GR, Tiffany-Castiglioni E. Differential ability of astroglia and neuronal cells to accumulate lead: dependence on cell type and on degree of differentiation. Toxicol Sci 1999; 50: 236-43.
29	In vitro rat neurons, 1' cell culture	--	CNS astrocytes	Immature astroglia but not mature neurons sequester lead preferentially	Reservoir for later continuous release of Pb leading to damage of nearby neurons.	Holtzman D, Olson JE, DeVries C, Bensch J. Lead toxicity in primary cultured cerebral astrocytes and cerebellar granular neurons. Toxicol Appl Pharmacol 1987; 89: 211-25.
30	Rats, in vivo	--	CNS astrocytes	Astrocytes modulate synaptic activity and potential excitotoxicity by converting glutamate to glutamine.	Astrocytes as a target for lead effects.	Norenberg MD & Martinez-Hernandez A. Fine structural localization of glutamine synthetase in astrocytes in rat brain. Brain Res 1979; 161: 303-10.
31	Cell culture Astrocytes	5.0 to 20	2nd Messenger System Effects	Dose & time dependent ↓ in glutamine synthetase activity with 7-21 culture exp. affects modulation of synaptic activity & potential excitotoxicity.	Astroglial function is vulnerable to low level Pb exp.	Sierra EM & Tiffany-Castiglioni, E. Reduction of glutamine synthetase activity in astroglia exposed in culture to low levels of inorganic lead. Toxicology 1991; 65: 295-304.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
32	Rats, in vivo	38.2 blood 0.03 µg/g brain tissue	Direct CNS cell effects	Myelin from brains in lead-poisoned rats was morphologically abnormal. Oligodendrocytes were grossly abnormal.	Brain abnormalities. Impaired brain function. Most CNS myelination occurs in first 2 months of life, so children may be more sensitive to this effect	Dabrowska-Bouta B, Sulkowski G, Bartosz G, Walski M, Rafalowska U. Chronic lead intoxication affects the myelin membrane status in the central nervous system of adult rats. J Mol Neurosci 1999; 13: 127-39.
33	Young rats, in vivo	38.2	Direct CNS cell effects	Decrease in activity of CNPase, an enzyme necessary for myelin synthesis during development.	Myelination impairment leading to cell function decreases.	Dabrowska-Bouta B, Sulkowski G, Walski M, Struzynska L, Lenkiewicz A, Rafalowska U. Acute lead intoxication in vivo affects myelin membrane morphology and CNPase activity. Exp Toxicol Pathol 2000; 52: 257-63.
34	Review Paper	--	Direct CNS cell effects	Delayed maturation of oligodendroglia.	Neuroglia (astrocytes & oligodendroglia) are 1' target of lead toxicity.	Tiffany-Castiglioni E, Sierra EM, Wu J-N, Rowles TK. Lead toxicity in neuroglia. [Review]. Neurotoxicol 1989; 10: 417-43.
35	In vivo, rats	--	Direct CNS cell effects	Direct toxic effects on Schwann cells.	Affects neurotransmission.	Dyck PJ, O'Brien PC, Ohnishi A. Lead neuropathy: Random distribution of segmental demyelination among 'old internodes' of myelinated fibers. J Neuropathol Exp Neurol 1977; 36: 570-5.
36	Humans, umbilical chord blood	0.9-10.1	Fetal Exposure	Direct Pb exposure of fetus from maternal blood lead.	Maternal exposure results in body burdens that result in breast fed infant exposures when Pb stored in bone is mobilized during lactation.	Gulson BL, Pounds JG, Mushak P, Thomas BJ, Gray B, Korsch MJ. Estimation of cumulative lead release (lead flux) from the maternal skeleton during pregnancy and lactation. J Lab Clin Med 1999; 134: 631-40.
37	Humans, breast milk	13.2 maternal, 6.9 chord	Breast Milk Contamination	Direct Pb exposure of fetus from maternal blood lead.	Pb stored in bone is mobilized during lactation, resulting in breast fed infant exposures	Li PJ, Sheng YZ, Wang QY, Gu LY, Wang YL. Transfer of lead via placenta and breast milk in human. Biomed Environ Sci 2000; 13: 85-9.
38	Humans, Epidemiological	3-10	MDI, Mental Development Index	--	Deleterious effects on cognitive development	Bellinger DC. Effect modification in epidemiological studies of low-level neurotoxicant exposures and health outcomes. [Review]. Neurotoxicol Teratol 2000; 22: 133-40.

	Study Design	Pb_B [µg/dl]	System Endpoint	Mechanism	Biological Significance	Reference
39	6-7 yr old children	4.3	Neuro-Psychological	--	Impaired attention span, visual perception, visual memory, finger tapping & reaction time all normal.	Walkowiak J, Altmann L, Kramer U, Sveinsson K, Turfedl M, Weishoff-Houben M. Cognitive & sensory-motor function in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol Teratol 1998; 20: 511-21.
40	9 yr old children	< 8	Neurological Function	Impaired visual-spatial constructional ability, decreased fine motor function		Stiles KM & Bellinger DC. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. Neurotoxicol Teratol 1993; 15: 27-35.
41	6 yr old children, epidemiologic	7.28	Motor Function	Neonatal blood Pb levels inversely correlated with fine motor function, upper limb speed and dexterity. Postnatal exposure inversely correlated with bilateral coordination, upper limb speed, dexterity, and visual-motor functioning.		Deitrich KN, Berger OG, Succop PA,. Lead exposure and motor developmental status of urban six-year-old children in the Cincinnati Prospective Study. Pediatrics 1993; 91: 301-7